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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/950,016	09/10/2001	Janet A. Warrington	03848-00093	9580

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 01/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/950,016	WARRINGTON ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7-14,18-25 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7-14,18-25 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 25, 2004 has been entered.

2. Claim 37 has been added, and claims 1-2, 7-14, 18-25 and 37 are now pending and under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-2, 7-14, 18-25, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of diagnosing oral cancer in a human subject that comprise detecting an altered level of expression of any of the nucleic acids/genes recited in independent claims 1, 2, 7 and 22 other than the molecule described as "lysophospholipase-like," and for methods of monitoring the expression of said nucleic acids/genes, does not reasonably provide enablement for methods of diagnosing oral cancer or of monitoring expression levels in which any "lysophospholipase-like" molecule is detected, or for methods of "monitoring the progression" of oral cancer in a subject in which marker expression levels at different

time points are detected in order to "monitor the progression of oral cancer." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-2 are drawn to methods of monitoring gene expression in which arrays of probes are used to determine the relative hybridization/relative binding of array probes to nucleic acids derived from cells from malignant oral tissue. Claims 7-14,18-21, and 37 are drawn to methods of diagnosing oral cancer in which differences in levels of expression of markers in a subject sample as compared to a control sample are indicative of cancer. Claims 22-25 are drawn to methods of monitoring the progression of oral cancer in which the levels of markers are detecting at multiple time points and compared "in order to monitor the progression of oral cancer."

It is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the instant claims. The specification discloses particular groups of genes that were found to be upregulated and downregulated in oral cancer tissue samples taken from human subjects (see pages 19-23, Figure 2), and discloses that the results obtained by microarray analysis were confirmed by real-time PCR (see pages 23-24). Given the data provided in the specification, upregulation of one or more of the genes found by Applicants to be upregulated in oral cancers, and/or down regulation of one or more of the genes found by Applicants to be downregulated in oral cancers, are clearly among factors that one of skill in the art would reasonably consider in diagnosing oral cancer in a human subject. However, one of the molecules encompassed by the instant claims is described only as "lipophospholipase-like." Unlike the other molecules encompassed by the claims, there is no particular, well-known gene or nucleic acid that corresponds to this designation. Further, the claims themselves do not contain any further descriptive information (for example, a particular nucleotide sequence) that would allow one of skill in the art to identify a particular "lysophospholipase-like" human gene that is encompassed by the claims. Rather, the claims as written are sufficiently broad so as to encompass any human gene that might be considered by one of skill in the art to be "lysophospholipase-like." While one of skill in the art could conduct further experimentation aimed at determining what particular "lysophospholipase-like" molecules are related to oral cancer, the outcome of such experimentation cannot be predicted, and it is thus unpredictable as to what type(s) of "lysophospholipase-like" genes/nucleic acids could

actually be employed in the practice of applicant's invention. Accordingly, it would require undue experimentation to make and use applicant's invention as now claimed.

Further, with regard to claims 22-25, applicant's specification provides no evidence that various levels of expression, e.g., correlate with tumor stage in any type of subject, as would be necessary in order for one to monitor tumor progression by detecting marker expression levels at various time points. As discussed in the prior Office actions of July 30, 2003 and June 24, 2004, the prior art as exemplified by Ibrahim et al (Oral Oncology 35:302-313 [5/1999]) discloses that no statistically significant correlation was found between tumor grade and expression levels of a group of oral cancer markers examined in oral cancer tissues taken from patients with different grades of tumors (see entire reference, particularly pages 308-309). Accordingly, neither the specification nor the prior art provide evidence that one could monitor progression of oral cancer in a subject by detecting expression levels of any type of oral cancer associated gene at various time points, and it is unpredictable as to whether any quantity of experimentation would allow a skilled artisan to practice such methods. Thus, it would require undue experimentation to use Applicants' invention in a manner reasonably commensurate with the instant claims.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-2, 7-14, 18-25, and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 7-14, 18-25, and 37 are indefinite over the recitation of a gene/nucleic acid identified only as "lysophospholipase-like" in claims 1, 2, 7, and 22. Neither the specification nor the prior art provide a clear definition of this terminology that would allow one of skill in the art to identify the molecule or molecules that correspond(s) to this designation. Accordingly, it is not clear what molecule(s) is/are encompassed by the claims.

Claim 1 is indefinite over the recitation of the phrase "wherein nucleic acids that hybridize differently correspond to genes of a gene expression profile that are associated with oral cancer, and wherein the genes of a gene expression profile are selected from the group consisting of....epithelial membrane protein 1." First, it is not clear what type of relationship or relationships between the "nucleic acids" of the claim and the "genes of a gene expression profile" is indicated or encompassed by the term "correspond." More particularly, it is not clear whether the language "nucleic acids...correspond to genes of a gene expression profile" indicates that any nucleic acids identified via the practice of the method are considered to define or constitute a particular "gene expression profile" consisting of a subset of the genes recited in the claim, whether this language merely makes reference to a pre-existing pool of genes considered to be a "gene expression profile" from which the nucleic acids of the claim may be selected, etc. Further, it is unclear from this language whether the determination of a single nucleic acid that hybridizes "differently" would be sufficient to meet the claim. Particularly, while the claim recites a group of genes from which "genes of a gene expression profile" may be selected (such that the claim clearly does not

require all of the genes recited therein), the use of the plural terms "nucleic acids" and "genes" appears to indicate that multiple nucleic acids/genes of that group are necessary. Clarification is required.

Claim 2 is indefinite over the recitation of the phrase "the nucleic acid corresponds to a gene selected from..." it is not clear what type of relationship or relationships between the "nucleic acid" of the claim and the "gene" of the claim is indicated or encompassed by the term "correspond." For example, does this language mean that the nucleic acid is a gene, that it is, e.g., a transcription product of the gene, that it is, e.g., a fragment or variant of the gene, etc. Clarification is required.

Claims 7-14, 18-25, and 37 are indefinite over the recitation of the phrase "the group of markers associated with oral cancer corresponds to a group of genes comprising..." in claims 7 and 22. It is not clear what type of relationship or relationships between the "group of markers" of the claims and the "group of genes" of the claims is indicated or encompassed by the term "corresponds." For example, does this language mean that the "group of markers" is a "group of genes," or would the claims encompass, e.g., other molecules structural related to or linked to members of the "group of genes," etc. Clarification is required.

Claim Rejections - 35 USC § 103

7. It is noted that the following rejections have been withdrawn in view of Applicants' amendment of claims 1, 2, and 7 to require the particular genes now listed in those claims:

a) the rejection of claims 1-2, 7-9, 11-14, and 18-21 as being unpatentable over Levine et al in view of Chang et al; and

b) the rejection of claim 10 as being unpatentable over Levine et al in view of Chang et al and Ts'o et al.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday-Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached at 571/272-0745. The fax phone number for the organization where this application or proceeding is assigned is 571/273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Diana B. Johannsen

Diana B. Johannsen
Primary Examiner
January 9, 2005